(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 December 2004 (09.12.2004)

PCT

(10) International Publication Number
WO 2004/105738 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number:
PCT/EP2004/005064

(22) International Filing Date: 12 May 2004 (12.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/EP03/05662 30 May 2003 (30.05.2003) EP

(71) Applicant *(for all designated States except US)*: **ACTELION PHARMACEUTICALS LTD** [CH/CH]; Gewerbestrasse 16, CH-4123 Allschwil (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BUR, Daniel** [CH/CH]; Im Rosengarten 24, CH-4106 (CH). **FISCHLI, Walter** [CH/CH]; Obertorweg 64, CH-4123 Allschwil (CH). **REMEN, Lubos** [SK/CH]; Kurzelängeweg 28, CH-4123 Allschwil (CH). **RICHARD-BILDSTEIN, Sylvia** [FR/FR]; 12, rue des Beaux Prés, F-68440 Dietwiller (FR). **WELLER, Thomas** [CH/CH]; Hoelzlistrasse 32b, CH-4102 Binningen (CH). **BOSS, Christoph** [CH/CH]; Muesmattweg 98, CH-4123 Allschwil (CH). **BINKERT, Christoph** [CH/CH]; In den Ziegelhoefen 89, CH-4054 Basel (CH). **MEYER, Solange** [FR/FR]; 10a, Rue Du Ruisseau, F-68440 Schlierbach (FR).

(74) Agent: **HOFMANN, Dieter**; Therwilerstrasse 87, CH-4153 Reinach (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE OF TETRAHYDROPYRIDINE DERIVATIVES

(57) Abstract: The invention relates to tetrahydropyridine derivatives and related compounds and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of plasmepsin II.

WO 2004/105738 A2

Use of Tetrahydropyridine Derivatives

In an earlier patent application, first published as WO 04/002957 A1 (Actelion Pharmaceuticals Ltd) novel tetrahydropyridine derivatives and their preparation as well as their use, especially as renin inhibitors, have been described. It has now been found that these compounds inhibit plasmepsin II. They are therefore useful as antimalarials.

The present invention is concerned with the use of tetrahydropyridine derivatives against malaria pathogens and, in particular, relates to compounds of the general formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula I and especially their use as plasmepsin II inhibitors for the treatment of malaria. Furthermore, these compounds can be regarded as inhibitors of other aspartyl proteases and might, therefore, be useful as inhibitors of plasmepsin I, plasmepsin IV or histo-aspartic protease (HAP) to treat malaria and as inhibitors of *Candida albicans* secreted aspartyl proteases to treat fungal infections.

Background of the invention:

Malaria is one of the most serious and complex health problems affecting humanity in the 21st century. The disease affects about 300 million people worldwide, killing 1 to 1.5 million people every year. Malaria is an infectious disease caused by four species of the protozoan parasite Plasmodium, P. falciparum being the most severe of the four. All attempts to develop vaccines against P. falciparum have failed so far. Therefore, therapies and preventive measures against malaria are confined to drugs. However, resistance to many of the currently available antimalarial drugs is spreading rapidly and new drugs are needed.

P. Falciparum enters the human body by way of bites of the female anophelino mosquito. The plasmodium parasite initially populates the liver, and during later

stages of the infectious cycle reproduces in red blood cells. During this stage, the parasite degrades hemoglobin and uses the degradation products as nutrients for growth [1]. Hemoglobin degradation is mediated by serine proteases and aspartic proteases. Aspartic proteases have been shown to be indispensable to parasite growth. A non-selective inhibitor of aspartic proteases, Pepstatin, inhibits the growth of P. falciparum in red blood cells in vitro. The same results have been obtained with analogs of pepstatin [2], [3]. These results show that inhibition of parasite aspartic proteases interferes with the life cycle of P. falciparum. Consequently, aspartic proteases are targets for antimalarial drug development.

The present invention relates to the identification of low molecular weight, non-peptidic inhibitors of the plasmodium falciparum protease plasmepsin II or other related aspartic proteases to treat and/or prevent malaria.

Prior Art:

To date several classes of plasmepsin II inhibitors have been described in the literature. To the best of our knowledge, none of these compounds has entered clinical development so far. Research efforts within different structural classes of plasmepsin II inhibitors have recently been summarized and published [C. Boss et al.; *Curr. Med. Chem.* **2003**, *10*, 883-907 and references cited there]. Plasmepsin inhibitors based on a peptidomimetic or substrate-analogue approach are described in the following patents: US-05734054 (Pharmacopeia Inc), US-05892038 (Pharmacopeia Inc.), WO-00114331 (University of California, Berkley), WO-02074719 (Johns Hopkins University), and publications: D. Nöteberg, E. Hamelink, J. Hulten, M. Wahlgren, L. Vrang, B. Samuelsson, A. Hallberg, *J. Med. Chem.*, **2003**, *46*, 734-746. K. Oscarsson, S. Oscarson, L. Vrang, E. Hamelink, A. Hallberg, B. Samuelsson, *Bioorg. Med. Chem.*, **2003**, *11*, 1235-1246. A. Dahlgren, I. Kvarnström, L. Vrang, E. Hamelink, A. Hallberg, A. Rosenquist, B. Samuelsson, *Bioorg. Med. Chem.*, **2003**, *11*, 827-841. Non-peptidomimetic plasmepsin II inhibitors are described in the following publications: WO-00224649 (Actelion Pharmaceuticals Ltd.), WO-00238543 (Actelion Pharmaceuticals Ltd.) and WO-09912532 (F. Hoffmann-LaRoche Ltd.).

Only one publication was found so far that describes non-peptidomimetic, rationally designed plasmepsin II inhibitors: Carcache, D. A.; Hörtner, S. R.; Bertogg A.; Binkert, C.; Bur, D.; Märki, H.-P.; Dorn, A.; Diederich, F.; *ChemBioChem*, **2002**, *11*, 1137.

The compounds of general formula I were tested against plasmepsin II, HIV-protease, human cathepsin D, human cathepsin E and human renin in order to determine their biological activity and their selectivity profile.

In vitro Assays:

The fluorescence resonance energy transfer (FRET) assay for HIV, plasmepsin II, human cathepsin D and human cathepsin E.

The assay conditions were selected according to reports in the literature [4 - 7]. The FRET assay was performed in white polysorp plates (Fluoronunc, cat n° 437842 A). The assay buffer consisted of 50 mM sodium acetate pH 5, 12,5% glycerol, 0.1% BSA + 392 mM NaCl (for HIV-protease).
The incubates per well were composed of:

- 160 µl buffer
- 10 µl inhibitor (in DMSO)
- 10 µl of the corresponding substrate in DMSO (see table A) to a final concentration of 1 µM
- 20 µl of enzyme to a final amount of x ng per assay tube (x = 10 ng/assay tube plasmepsin II, x = 100 ng/assay tube HIV-protease, x = 10 ng/assay tube human cathepsin E and x = 20 ng/assay tube human cathepsin D)

The reactions were initiated by addition of the enzyme. The assay was incubated at 37°C for 30 min (for human cathepsin E), 40 min (for plasmepsin II and HIV-protease) or 120 min (for human cathepsin D). The reactions were stopped by adding 10% (v/v) of a 1 M solution of Tris-base. Product-accumulation was monitored by measuring the fluorescence at 460 nm.

Auto-fluorescence of all the test substances is determined in assay buffer in the absence of substrate and enzyme and this value was subtracted from the final signal.

Aspartyl protease	substrate		enzyme concentration ng/at (nM)	Buffer	pH	incubation time minutes
	sequence	substrate concentration µM				
HIV	Dabcyl-Abu-SQNY:PIVN-EDANS	1	100 (22.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1 % BSA 392 mM NaCl	5	40
Plasmepsin II	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	40
h Cathepsin D	Dabcyl-ERNleF:LSFP-EDANS	1	20 (2.5)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	120
h Cathepsin E	Dabcyl-ERNleF:LSFP-EDANS	1	10 (1.25)	50 mM Na acetate ; 12,5 % glycerol ; 0.1% BSA	5	30

Table A: Summary of the conditions used for the aspartyl proteases fluorescent assays. (at = assay tube)

References:

1. Goldberg, D. E., Slater, A. F., Beavis, R., Chait, B., Cerami, A., Henderson, G. B.; *J. Exp. Med.*, **1991**, *173*, 961 – 969.

2. Francis, S. E., Gluzman, I. Y., Oksman, A., Knickerbocker, A., Mueller, R., Bryant, M. L., Sherman, D. R., Russell, D. G., Goldberg, D. E.; *Embo. J.*, **1994**, *13*, 306 – 317.

3. Moon, R. P., Tyas, L., Certa, U., Rupp, K., Bur, D., Jaquet, H., Matile, H., Loetscher, H., Grueninger-Leitch, F., Kay, J., Dunn, B. M., Berry, C., Ridley, R. G.; *Eur. J. Biochem.*, **1997**, *244*, 552 – 560.

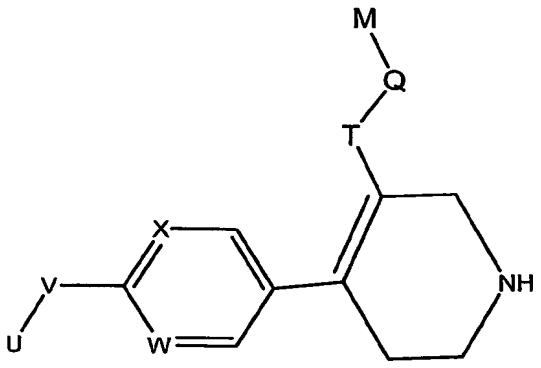
4. Carroll, C. D., Johnson, T. O., Tao, S., Lauri, G., Orlowski, M., Gluzman, I.Y., Goldberg, D. E., Dolle, R. E., *Bioorg Med Chem Lett* ; **1998**, *8*, 3203 – 3206.

5. Peranteau, A. G., Kuzmic, P., Angell, Y., Garcia-Echeverria, C., Rich, D. H., *Anal Biochem*; **1995**, *227*(1), 242 – 245.

6. Gulnik, S. V., Suvorov, L. I., Majer, P., Collins, J., Kane, B. P., Johnson, D. G., Erickson, J. W., *FEBS Lett*; **1997**, *413*(2), 379 – 384.

7. Robinson, P. S., Lees, W. E., Kay, J., Cook, N. D., *Biochem J*; **1992**, *284* (Pt 2), 407 – 409.

In particular, the present invention relates to pharmaceutical compositions for treating diseases demanding the inhibition of parasitic aspartic proteases containing one or more compounds of the general formula **I**,



Formula I

wherein

X and W represent independently a nitrogen atom or a CH-group;

V represents $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; $-CH_2-CH_2-A-CH_2-CH_2-B-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; -COO-; $-(CH_2)_pOCONR^1-$; $-(CH_2)_pN(R^{1'})CONR^1-$;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

R^1 and $R^{1'}$ independently represent hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5 or 6;
s is the integer 2, 3, 4 or 5;
t is the integer 1, 2, 3 or 4;
u is the integer 1, 2 or 3;
v the integer to 2, 3 or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms and suitable carrier materials.

In the definitions of general formula I – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

The term **lower alkoxy** refers to a R-O group, wherein R is a lower alkyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and two to seven

carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl or butenyl.

The term **lower alkinyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkinyl are ethinyl, propinyl or butinyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkylene are ethylene, propylene or butylene.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkylenoxy** refers to a lower alkylene substituted at one end by an oxygen atom. Examples of lower alkylenoxy groups are preferably ethylenoxy and propylenoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl,

cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono-, di-, or trisubstituted independently by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy, lower alkylenoxy, lower alkylenedioxy, hydroxy, halogen, $-CF_3$, $-NR^1R^{1'}$, $-NR^1C(O)R^{1'}$, $-NR^1S(O)_2R^{1'}$, $-C(O)NR^1R^{1'}$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$. The cyclopropyl group is a preferred group.

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl group, preferably the phenyl group, which can be optionally mono-, di-, tri-, tetra- or pentasubstituted independently by lower alkyl, lower alkenyl, lower alkinyl, lower alkenylene or lower alkylene forming with the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylenedioxy, lower alkylenoxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-NR^1C(O)R^{1'}$, $-NR_1S(O)_2R^{1'}$, $-C(O)NR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-S(O)R^1$, $-S(O)_2R^1$, $-SO_2NR^1R^{1'}$, benzyloxy. Prefered substituents are halogen, lower alkoxy, lower alkyl.

The term **aryloxy** refers to an Ar-O group, wherein Ar is an aryl. An example of aryloxy groups is phenoxy.

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or sulfur atoms which may be the same or different and which rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms, if present, can be substituted by a $COOR^2$ group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic

rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequatly substituted with lower alkyl, lower alkenyl, lower alkinyl, lower alkylene, lower alkenylene, lower alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-N(R^1)COR^1$, $-N(R^1)SO_2R^1$, $-CONR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-S(O)R^1$, $-S(O)_2R^1$, $-SO_2NR^1R^{1'}$, another aryl, another heteroaryl or another heterocyclyl and the like.

The term **heteroaryloxy** refers to a Het-O group, wherein Het is a heteroaryl.

It is understoood that the substituents outlined relative to the expressions cycloalkyl, heterocyclyl, heteroaryl and aryl have been omitted in the definitions of the general formula **I** and in claims 1 to 6 for clarity reasons but the definitions in formula **I** and in claims 1 to 6 should be read as if they are included therein.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non toxic to living organisms or in case the compound of formula **I** is acidic in

nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of the general formula **I** can contain one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts therof.
The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

Especially preferred compounds of the invention are listed in table 1 below (page 51).

The compounds of general formula **I** and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. These pharmaceutical compositions may particularly be used for treatment of disorders associated with the role of plasmepsin II and which require inhibition of plasmepsin II for treatment. They may especially be used for treatment and/or prevention of malaria or diseases caused by protozoal infection. These pharmaceutical compositions may also contain aside of one or more compounds of the general formula I a known plasmepsin II inhibitor, a known antimalarial or known HIV protease inhibitor.

Further, these pharmaceutical compositions may also be used for treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases, and particularly for malaria or protozoal infections.

The invention also relates to the use of pharmaceutical compositions as defined above for the treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases in combination with a known plasmepsin II inhibitor, a

known antimalarial or a known HIV protease inhibitor or another known anti-HIV treatment.

In addition, compounds of formula I are useful for the preparation of a medicament for the treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases, particularly malaria or protozoal infection. These compounds are more particularly useful for diseases demanding the inhibition of parasitic aspartic proteases in combination with a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor or another known anti-HIV treatment.

Another aspect of the invention concerns a method of treating a patient suffering from a disease requiring the inhibition of parasitic aspartic proteases by administering a pharmaceutical composition comprising a compound of the general formula I. The dosage of compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage between 1 mg and 1000 mg, particularly between 50 mg and 500 mg, comes into consideration.

The pharmaceutical preparations conveniently contain between 1 mg and 500 mg, preferably between 5 mg and 200 mg of a compound of formula I.

A further aspect of the invention concerns a process for the preparation of the above-mentioned pharmaceutical composition by mixing one or more active ingredients of formula I with inert excipients in a manner known per se.

The compounds of formula I may also be used in combination with one or more other therapeutically useful substances.

All forms of prodrugs leading to an active component comprised in general formula I are included in the present invention.

The compounds of general formula I can be manufactured by the methods given in another patent application filed by the applicant (Actelion Pharmaceuticals Ltd).

The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical preparations for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants in a manner known per se.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injections are, for

example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of compounds of formula **I** can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration. For children the dosage has to be adapted to the body weight and age.

The pharmaceutical preparations conveniently contain about 1 - 500 mg, preferably 5 - 200 mg of a compound of formula **I**.

The compounds of general formula **I** can be manufactured by the methods given below, by the methods given in the examples of WO 04/002957 A1 (Actelion Pharmaceuticals Ltd.) or by analogous methods.

Synthetic Approaches for the preparation of compounds of general formula I:

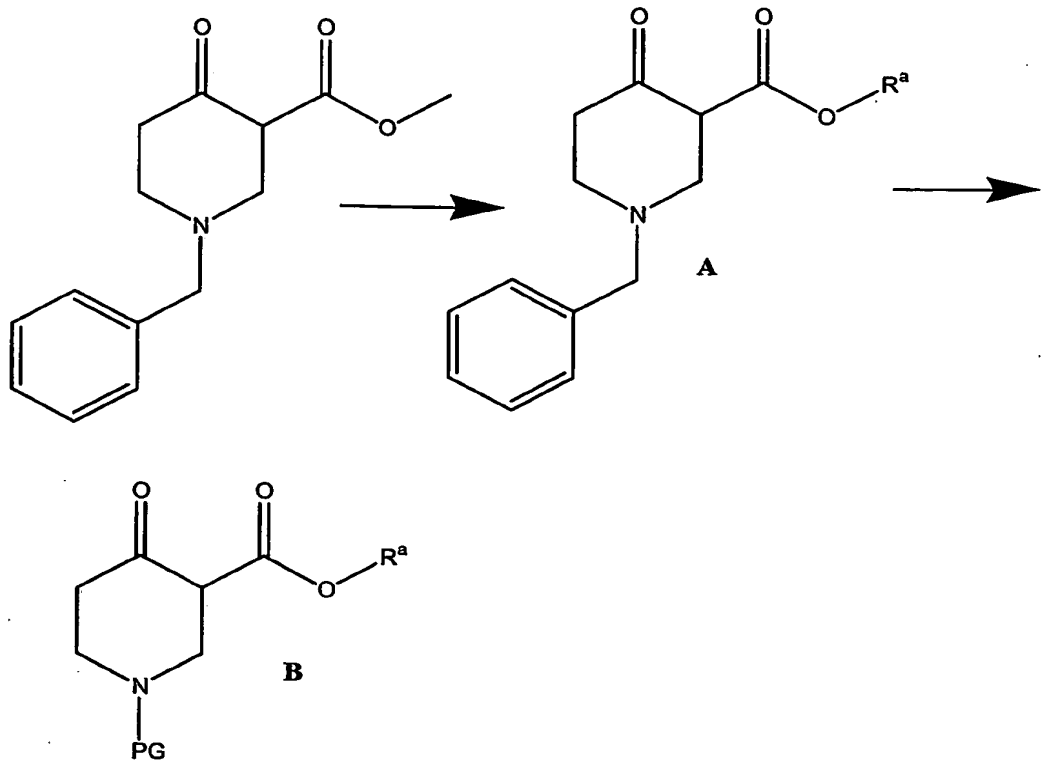
The final compounds were characterized at least by LC-MS and ^{1}H-NMR. Only the LC-MS data are given in the earlier application filed by the applicant (Actelion Pharmaceuticals Ltd.).

Preparation of the precursors:

Precursors are compounds that were prepared as key intermediates and/or building blocks and which were suitable for further transformations in parallel chemistry.

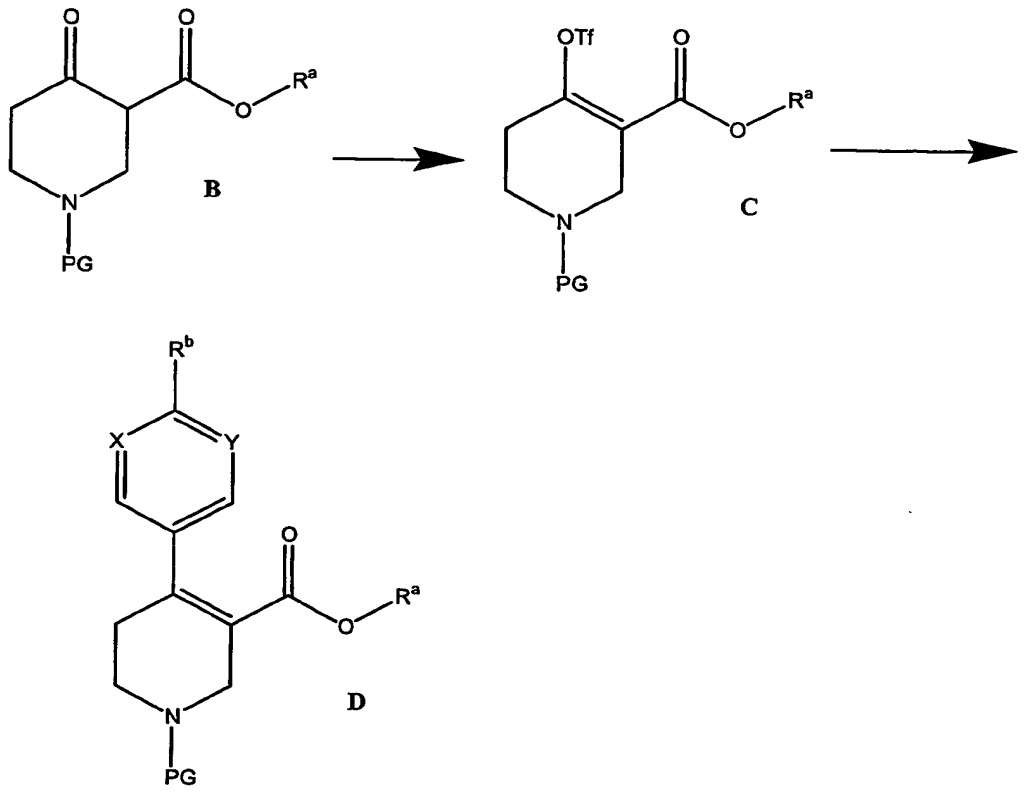
Ideal starting materials are any commercially available 4-oxo-piperidine-3-carboxylic acid ester derivatives, for instance 1-benzyl-4-oxo-piperidine-3-carboxylic acid methyl ester, possibly as a salt. For practical purposes, a transesterification (for instance according to Seebach D., *et al.*, *Synthesis*, **1982**, 138) to another ester derivative **A** (wherein R^a is optionally a lower alkyl, a lower alkenyl, or a benzyl group), thereafter a change in the *N*-protecting group (PG: all abreviations are outlined at the beginning of the chapter Examples) to a derivative of type **B**, may be necessary (Scheme 1).

Scheme 1



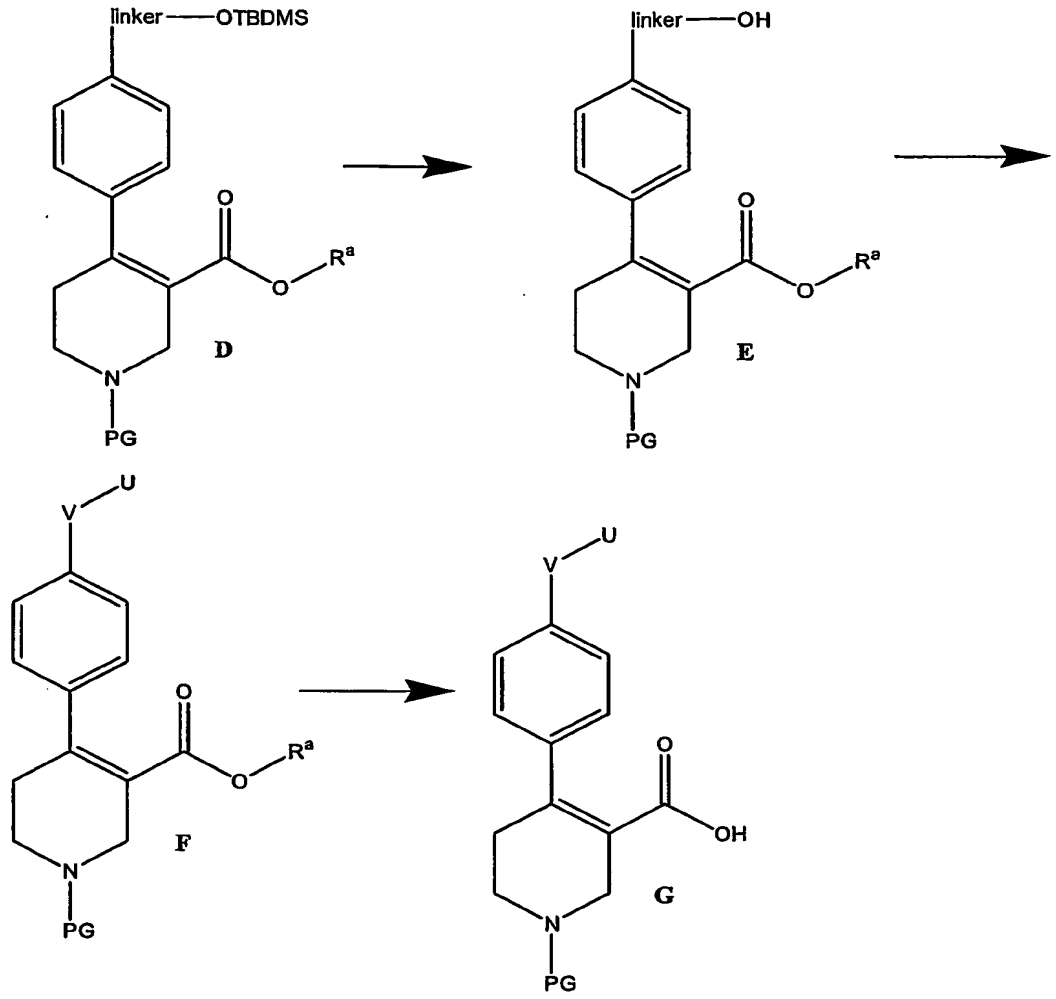
Formation of the vinyl triflate **C**, followed by a coupling catalysed by a Pd(0) complex may lead to tetrahydropyridine derivatives of type **D**, wherein R^b optionally represents any U-V group as defined in general formula **I** or a chemical precursor of such a group (Scheme 2).

Scheme 2



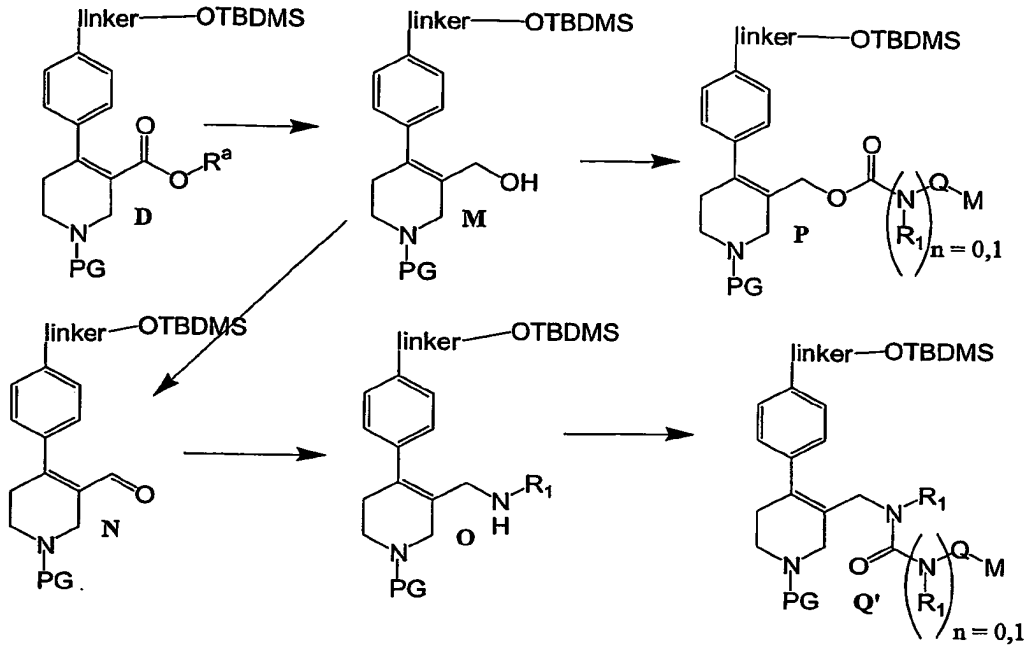
If, for instance, R^b is a linker ending with a silanyl ether, compounds of type **D** are deprotected to compounds of type **E**, then coupled to a phenol or aromatic alcohol using a *Mitsunobu* reaction, leading to derivatives of type **F** wherein V and U have the meaning given in general formula **I** above (Scheme 3). The ester **F** is optionally then be cleaved by any suitable method to lead to precursor **G**.

Scheme 3



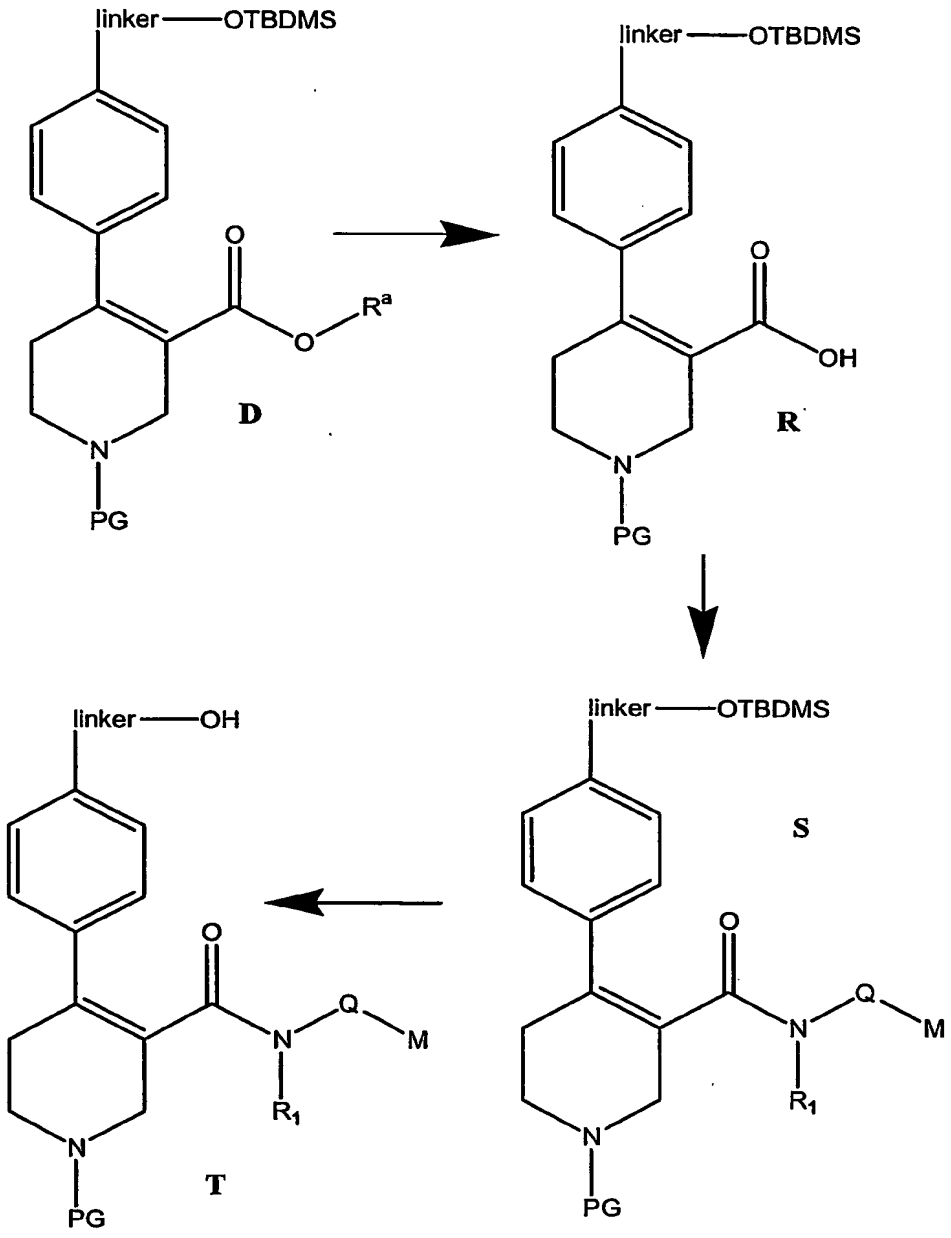
Also, a compound of type **D** may be reduced with DIBAL to a compound of type **M** that can be then oxidized to a compound of type **N** with e.g. the Dess-Martin periodinane (Scheme 4). Aldehyde **N** may then be transformed to a compound of type **O** by reductive amination, which can be acylated to a derivative of type **Q'** wherein Q and M have the meaning given in general formula **I** above. On the other hand, compounds of type **M** can be then acylated following standard procedures to esters or carbamates of type **P**.

Scheme 4



Also, as shown in Scheme 5, a precursor of type **T** can be prepared in three steps from a compound of type **D**, by saponification (compound of type **R**), amide coupling (compound of type **S**) and finally desilylation.

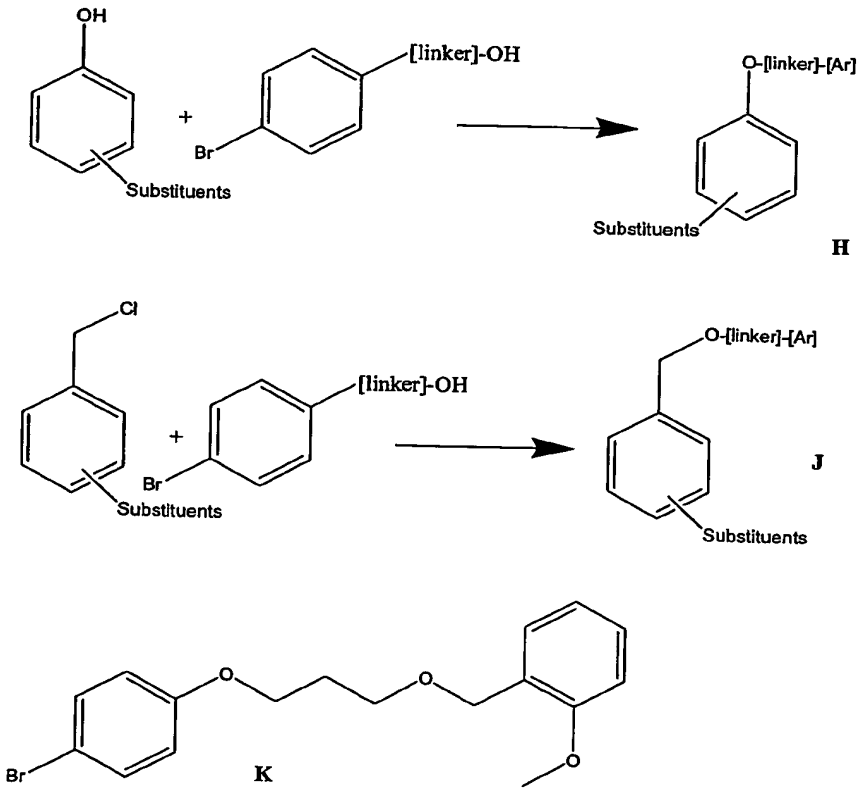
Scheme 5


linker—OTBDMS
O
O
R^a
N
PG
D
linker—OTBDMS
O
OH
N
PG
R
linker—OTBDMS
S
O
N
Q
M
R_1
N
PG
linker—OH
O
N
Q
M
R_1
N
PG
T

Preparation of bromoaryl derivatives

For the coupling of compounds of type **C** to tetrahydropyridine derivatives of type **D**, it can be necessary to prepare the bromoaryl components needed as described in Scheme 6. A *Mitsunobu* coupling (→ compounds of type **H**) or the alkylation of an alcohol with a benzylic chloride (or bromide, → compounds of type **J**) are often the most convenient methods. Derivative **K** was prepared in one step from 1-(3-chloropropoxymethyl)-2-methoxybenzene by reaction with 4-bromophenol (Vieira E. *et al.*, *Bioorg. Med. Chem. Letters*, **1999**, *9*, 1397). Other methods for the preparation of ethers or thioethers, like a *Williamson* synthesis, might be used as well (see e.g. March, J, "Advanced Organic Chemistry", 5th ed., John Wiley and sons, 2001).

Scheme 6



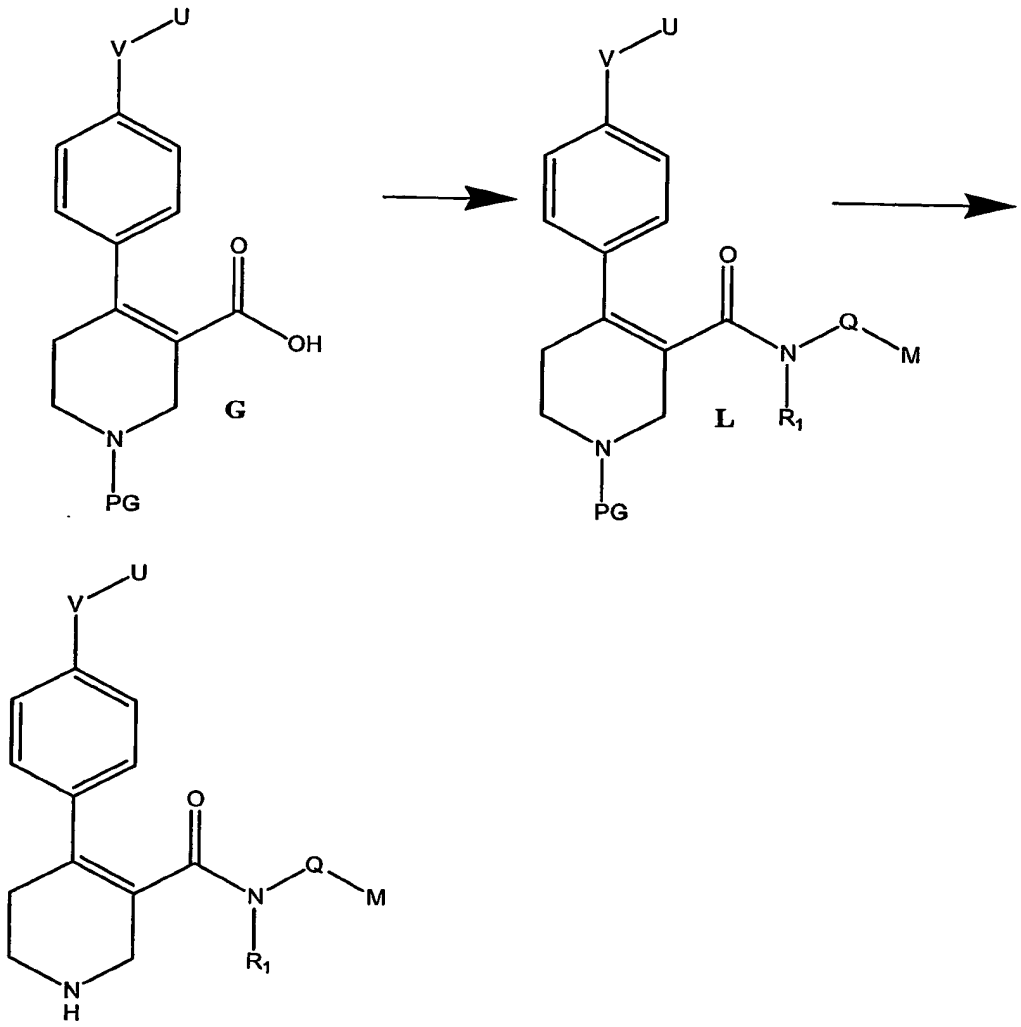
Preparation of the secondary amines

It may be necessary to prepare secondary amines as well. This can be done by reductive amination from the corresponding amine and aldehyde, or by amide coupling, from the corresponding amine and carboxylic acid, followed by reduction with LAH or borane. These standard procedures are well-described in the literature.

Preparation of final compounds

A compound of type **G** can be coupled to the amine to yield amides of type **L** wherein V, U and M have the meaning given in general formula **I** above. Removal of the *N*-protecting group (PG) leads to a final compound, wherein V, U, Q and M have the meaning given in general formula **I** above (Scheme 7).

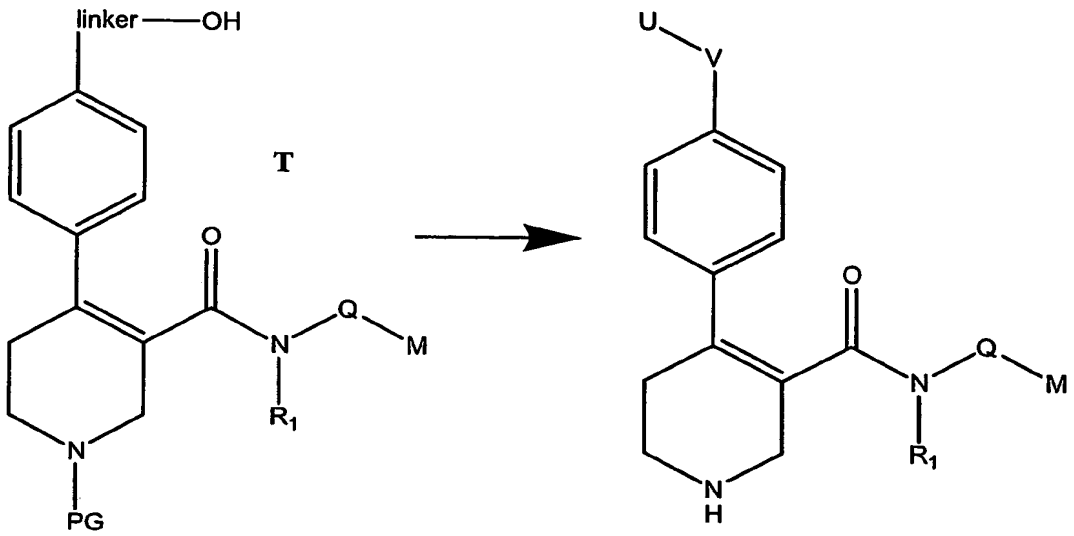
Scheme 7



Also, compounds of type **P** or **Q'** (Scheme 4) may be processed further as indicated in Scheme 3, then deprotected as indicated in Scheme 7, to lead to final compounds as defined in general formula **I**.

From a precursor of type **T** a final compound can be prepared by a *Mitsunobu*-type reaction, followed by deprotection (Scheme 8).

Scheme 8



General remarks

The following compounds were prepared according to the procedures described for the synthesis of compounds encompassed by the general formula **I**. All compounds were characterized by ^{1}H-NMR (300 MHz) and occasionally by ^{13}C-NMR (75 MHz) (Varian Oxford, 300 MHz), by LC-MS: **A**: 2 min < t_R < 10 min; (Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT; Column: 2x30 mm, Gromsil ODS4, 3 µM, 120A; Gradient: 0 - 100% acetonitril in water, 6 min, with 0.05% formic acid, flow: 0.45 mL/min; t_R given in min.), **B**: 0.1 min < t_R < 2 min; (Finnigan AQA with ESI-probe with HP 110 DAD and HP110 binary pump; column: Develosil RP-AQUEOUS, 5 µM, 4.6 mm x 50 mm; gradient: 5 - 95% methanol in water (0.04% TFA), 1 min, 95% methanol in water (0.04% TFA) 0.4 min, 4.5 mL/min.), by TLC (TLC-plates from Merck, Silica gel 60 F_{254}). LC-MS- and TLC-data only are given hereby.

Abbreviations

aq.	aqueous
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine serum albumine
BuLi	*n*-Butyllithium
conc.	Concentrated
DIBAL	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC·HCl	Ethyl-*N,N*-dimethylaminopropylcarbodiimide hydrochloride
EIA	Enzyme immunoassay
eq.	equivalent
Et	Ethyl

EtOAc	Ethyl acetate
FC	Flash Chromatography
HOBt	Hydroxybenzotriazol
LAH	Lithium aluminium hydride
MeOH	Methanol
org.	organic
PBS	Phosphate Buffer Saline
PG	protecting group
Ph	Phenyl
RP18	Reversed phase column, filled with C_{18} hydrocarbon
rt	room temperature
sol.	Solution
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMAD	*N,N,N',N'*-Tetramethylazodicarboxamide

General procedures

General procedure A for amide coupling

A sol. of the desired carboxylic acid (1.00 eq), the desired amine (2.00 eq), EDC·HCl (1.10 eq.), HOBt (cat. amount), DMAP (cat. amount) and DIPEA (2.00 eq.) in CH_2Cl_2 (20 mL/g of acid) was stirred at rt overnight. The reaction mixture was either washed over diatomic earth (Isolute Sorbent Technology, Johnson, C. R., *et al.*, Tetrahedron, **1998**, *54*, 4097), or washed with aq. 1M HCl, and the org. extracts were evaporated under reduced pressure. The residue was used without further purification.

General procedure B for the removal of a Boc-protecting group

The starting material was dissolved in CH_2Cl_2 (10 mL/g of starting material) and the sol. was cooled to 0°C. 4M HCl in dioxane (same volume as CH_2Cl_2) was added and the reaction mixture was left for 90 min at rt. The solvents were removed under reduced pressure. Purification of the residue by HPLC led to the desired compound.

Typical procedure C for amide formation from acid chlorides

To a sol. of the acid chloride (1 eq.) in CH_2Cl_2 (2.5 mL/mmol) at 0 °C. the amine (3 eq.) was added. The mixture was stirred for 3 h while warming up slowly to rt. If necessary, more CH_2Cl_2 was added, then the reaction mixture was washed with aq. sat. $NaHCO_3$ (1x) and aq. 1M HCl (1x). The extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. The obtained product was used without further purification.

Typical procedure D for the reduction of an amide to an amine with LAH

To a sol. of the amide (1 eq.) was dissolved in THF (3 mL/mmol) LAH (1M in THF, 3 eq.) was added carefully. The mixture was stirred at rt for 30 min, then heated to 60 °C for 3 h before it was allowed to cool down to rt, then to 0 °C. For x g of LAH initially added, was added x g of water, then x g of aq. 15% NaOH, and finally 3x g of water again. The resulting mixture was stirred overnight, filtered, and the precipitate washed with EtOAc. The filtrate was evaporated under reduced pressure and the residue diluted in a small amount of MeOH. The sol. was passed through a pad of SCX silica gel (sulfonic acid). Elution started with MeOH, followed by NH_3/MeOH. The amines eluted with the second second eluent. The solvents were removed under reduced pressure. The isolated amines were either used without further purification or purified by HPLC, depending on the purity.

Typical procedure E for reductive amination

To a solution of aldehyde (1eq.) in MeOH (0.5 mL/mmol) was added an amine (1.2 eq.). The solution was stirred for 2h. Sodium borohydride (1.2 eq.) was added portionwise at 0°C and then stirring was continued, at rt, for 4h. A solution of NaOH 1N was added and the MeOH was evaporated. The mixture was extracted with EtOAc twice and the organic layer was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. The isolated amines were either used without further purification or purified by flash chromatography (EtOAc/heptane: 2/8), depending on the purity.

Preparation of the secondary amines

(2-Chlorobenzyl)cyclopropylamine

Synthesized according to typical procedures C and D from 2-chlorobenzoyl chloride and cyclopropylamine.

(2-Chlorobenzyl)ethylamine

See Ishihara, Y; *et al.*; *Chem. Pharm. Bull.*, **1991**, *39*, 3225.

Cyclopropyl-(3,5-dimethoxybenzyl)amine

Synthesized according to typical procedure E from 2,5-dimethoxybenzaldehyde and cyclopropylamine.

Cyclopropyl-(2-fluoro-5-methoxybenzyl)amine

Synthesized according to typical procedure E from 2-fluoro-5-methoxybenzaldehyde and cyclopropylamine.

Cyclopropyl-(3-methoxybenzyl)amine

Synthesized according to typical procedure E from 3-methoxybenzaldehyde and cyclopropylamine.

Cyclopropyl-(3,4-dimethoxybenzyl)amine

Synthesized according to typical procedure E from 3,4-dimethoxybenzaldehyde and cyclopropylamine.

(2-Chloro-3-trifluoromethylbenzyl)cyclopropylamine

Synthesized according to typical procedure E from 2-chloro-3-trifluoromethylbenzaldehyde and cyclopropylamine.

(6-Chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamine

Synthesized according to typical procedure E from 6-chlorobenzo[1,3]dioxole-5-carbaldehyde and cyclopropylamine.

(2-Bromobenzyl)cyclopropylamine

Synthesized according to typical procedure E from 2-bromobenzaldehyde and cyclopropylamine.

Cyclopropyl-(2,3-dimethylbenzyl)amine

Synthesized according to typical procedure E from 2,3-dimethylbenzaldehyde and cyclopropylamine.

Cyclopropyl-(3,5-difluorobenzyl)amine

Synthesized according to typical procedure E from 3,5-difluorobenzaldehyde and cyclopropylamine.

(2,3-Dichlorobenzyl)cyclopropylamine

Synthesized according to typical procedure E from 2,3-dichlorobenzaldehyde and cyclopropylamine.

Cyclopropyl-(3-trifluoromethoxybenzyl)amine

Synthesized according to typical procedure E from 3-trifluoromethoxy-benzaldehyde and cyclopropylamine.

Cyclopropyl-(3-methylbenzyl)amine

Synthesized according to typical procedure E from 3-methylbenzaldehyde and cyclopropylamine.

(3-Chlorobenzyl)cyclopropylamine

Synthesized according to typical procedure E from 3-chlorobenzaldehyde and cyclopropylamine.

Cyclopropyl(2-fluorobenzyl)amine

Synthesized according to typical procedure E from 2-fluorobenzaldehyde and cyclopropylamine.

Cyclopropyl-(2-methylbenzyl)amine

Synthesized according to typical procedure E from 2-methylbenzaldehyde and cyclopropylamine.

Cyclopropyl-[2-(4-methoxyphenoxy)ethyl]amine

Synthesized according to typical procedures C and D from (4-methoxyphenoxy)-acetic acid and cyclopropylamine.

Cyclopropyl-[2-(3-methoxyphenoxy)ethyl]amine

Synthesized according to typical procedures C and D from (3-methoxyphenoxy)-acetic acid and cyclopropylamine.

Cyclopropyl-(2-*m*-tolyloxyethyl)amine

Synthesized according to typical procedures C and D from *m*-tolylacetic acid and cyclopropylamine.

[2-(2-Chlorophenyl)ethyl]cyclopropylamine

Synthesized according to typical procedures C and D from (2-chlorophenyl)-acetic acid and cyclopropylamine.

Cyclopropyl-[2-(4-fluorophenyl)ethyl]amine

Synthesized according to typical procedures C and D from (4-fluorophenyl)acetic acid and cyclopropylamine.

Cyclopropyl-(2-*o*-tolylethyl)amine

Synthesized according to typical procedures C and D from *o*-tolylacetic acid and cyclopropylamine.

Cyclopropyl-(2-*p*-tolylethyl)amine

Synthesized according to typical procedures C and D from *p*-tolylacetic acid and cyclopropylamine.

Preparation of the precursors

4-Oxopiperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (B)

A suspension of 1-benzyl-4-oxopiperidine-3-carboxylic acid methyl ester hydrochloride (5.00 g, 17.6 mmol), triethylamine (2.45 mL, 17.6 mmol) and Boc_2O (4.20 g, 20.0 mmol) in EtOH (30 mL) was purged with N_2. Pd/C (10%, 600 mg) was added and the suspension purged with H_2. The reaction mixture was stirred under an H_2-atmosphere for 24 h and then filtered through *Celite*. The filtrate was evaporated under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3) yielded the title compound (4.02 g, 89%). $R_f = 0.60$ (EtOAc/heptane 1:1). LC-MS: $R_t = 1.09$ min, ES+ = 202.03.

Compounds of type C

1-Benzyl-4-trifluoromethanesulfonyloxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid ethyl ester (C1)

To a suspension of 1-benzyl-4-oxo-piperidine-3-carboxylic acid ethyl ester hydrochloride (1.50 g, 5.04 mmol) in THF (30 mL) NaH (about 60% in oil, 600 mg, about 15 mmol) was added at 0°C. As the suspension turned thick CH_2Cl_2 (20 mL) was added. The ice bath was removed and Tf_2NPh (2.68 g, 7.50 mmol) was added. The mixture was stirred overnight and ice was added. The mixture was washed with aq. 10% Na_2CO_3 (1x) and the org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure and purification of the residue by FC (EtOAc/heptane 1:9 → 1:4 → 2:3) yielded the title compound (2.10 g, almost quantitative yield). R_f = 0.50 (EtOAc/heptane 1:1). LC-MS: R_t = 4.65 min, ES+: 394.12.

4-Trifluoromethanesulfonyloxy-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (C2)

To a sol. of compound **B** (4.00 g, 15.6 mmol) in THF (100 mL) at 0 °C was added NaH (suspension in oil, 55-65%, 1.20 g, about 31 mmol). The suspension was stirred for 30 min at 0 °C and Tf_2NPh (8.27 g, 23.1 mmol) was added. The ice bath was removed and the reaction mixture stirred for 3 days at rt. Ice was added and the solvents were removed under reduced pressure. The residue was diluted with EtOAc and washed with aq. 10% Na_2CO_3. The org. extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4) yielded the title compound (5.19 g, 86%). LC-MS: R_t = 1.17, ES+ = 374.96.

Compounds of type D

1-Benzyl-4-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid ethyl ester (D1)

To a sol. of 4-bromo-1-[3-(2-methoxybenzyloxy)propoxy]benzene (2.81 g, 8.01 mmol) in THF (50 mL) at -78 °C *n*-BuLi (1.5M in hexane, 5.60 mL, 8.41 mmol) was added. After 30 min $ZnCl_2$ (1M in THF, 9.00 mL, 9.00 mmol) was added and the mixture was allowed to warm up to rt. Vinyl triflate **C1** (2.10 g, 5.34 mmol) and $Pd(PPh_3)_4$ (154 mg, 0.134 mmol) were added and the mixture stirred at rt for 4.5 h. Ice was added, the mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:9 → 1:4 → 2:3 → 3:2) led to the title compound (2.25 g, 82%). R_f = 0.32 (EtOAc/heptane 1:1). LC-MS: R_t = 4.05 min, ES+ = 516.23.

4-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (D2)

To a sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183; 6.19 g, 19.7 mmol) in THF (100 mL) at -78 °C was added n-BuLi (1.5M in hexane, 14.0 mL, 21.0 mmol). The sol. was

stirred at -78 °C for 30 min and $ZnCl_2$ (1M in THF, 22.3 mL, 22.3 mmol) was added. The resulting sol. was allowed to warm to rt and compound **C2** (5.10 g, 13.1 mmol) and $Pd(PPh_3)_4$ (300 mg, 0.26 mmol) were added. After 20 min at rt ice was added to the reaction mixture. The solvents were removed under reduced pressure and the residue diluted with EtOAc. This mixture was washed with aq. 1M NaOH. The org. extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:9) led to the title compound (5.77 g, 90%). LC-MS: R_t = 7.27 min, ES+ = 512.54.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (D3)

As described for compound **D2** but from [2-(4-bromo-phenoxy)ethoxy]-*tert*-butyldimethylsilane (Morita, C.; et al.al.; *Heterocycles*, **2000**, *52*, 1163; 49.5 g, 149 mmol), BuLi (1.6M in hexane, 94 mL, 150 mmol), $ZnCl_2$ (1M in THF, 200 mL, 200 mmol), compound **C2** (37.0 g, 95 mmol), $Pd(PPh_3)_4$ (2.75 g, 2.38 mmol) and THF (750 mL). Purification by FC yielded the title compound (36.6 g, 78%). LC-MS: R_t = 1.20 min, ES+ = 492.34.

Compounds of type E

4-[4-(3-Hydroxypropyl)phenyl]-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (E1)

TBAF (1.90 g, 6.00 mmol) was added to a sol. of compound **D2** (1.95 g, 4.00 mmol) in THF (40 mL). The reaction mixture was stirred for 6 h at rt and diluted with EtOAc. The resulting mixture was washed with water and brine. The org. extracts were dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:3) yielded the title compound (1.27 g, 84%). LC-MS: R_t = 1.06, ES+ = 376.18.

4-[4-(2-Hydroxyethoxy)phenyl]-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester-3-methyl ester (E2)

As described for compound **E1** but from compound **D3** (5.63 g, 11.4 mmol), TBAF (5.41 g, 17.1 mmol) and THF (115 mL). Purification by FC yielded the title compound (3.46 g, 80%). LC-MS: R_t = 1.01; ES+ = 378.22.

Compounds of type F

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F1)

A sol. of compound **E1** (750 mg, 2.00 mmol), 2-bromo-5-fluorophenol (0.334 mL, 3.00 mmol), azodicarboxyl dipiperidide (757 mg, 3.00 mmol), tri-n-butylphosphine (0.987 mL, 4.00 mmol) and DIPEA (0.035 mL, 0.20 mmoL) in toluene (20 mL) was stirred for 1 h at rt, then for 2 h at 60 °C. The reaction mixture was allowed to cool to rt, was diluted with EtOAc and washed with water. The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7) led to the title compound (898 mg, 82%). LC-MS: R_t = 6.43 min, ES+ = 570.00.

4-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F2)

A sol. of compound **E1** (375 mg, 1.00 mmol), 2-chlorophenol (0.153 mL, 1.50 mmol), azodicarboxyl dipiperidide (378 mg, 1.50 mmol), tri-n-butylphosphine (0.493 mL, 2.00 mmol) and DIPEA (0.018 mL, 0.10 mmoL) in toluene (10 mL) was stirred for 1 h at rt, then for 2 h at 60 °C. The reaction mixture was allowed to cool to rt, was diluted with EtOAc and washed with water. The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced

pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7) led to the title compound (374 mg, 77%). LC-MS: R_t = 1.39 min, ES+ = 486.13.

4-{4-[3-(2,5-Difluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F3)

A sol. of compound **E1** (375 mg, 1.00 mmol), 2,5-difluorophenol (195 mg, 1.50 mmol), azodicarboxyl dipiperidide (378 mg, 1.50 mmol), tri-n-butylphosphine (0.493 mL, 2.00 mmol) and DIPEA (0.018 mL, 0.10 mmoL) in toluene (10 mL) was stirred for 1 h at rt, then for 2 h at 60 °C. The reaction mixture was allowed to cool to rt, was diluted with EtOAc and washed with water. The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7) led to the title compound (378 mg, 77%). LC-MS: R_t = 1.35 min, ES+ = 488.16.

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F4)

Prepared as described for compound **F1** but from compound **E1** (4.7 g, 12.5 mmol), 2,3,6-trifluorophenol (3.7 g, 25.0 mmol), azodicarboxyl dipiperidide (6.32 g, 34.2 mmol), tributylphosphine (85%, 9.3 mL, 37.6 mmol) and toluene (100 mL). Purification of the residue by FC yielded the title compound (5.23 g, 83%).

4-{4-[2-(2,3,5-Trimethylphenoxy)ethyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F5)

As described for compound **D2** but from compound **H1** (3.07 g, 9.63 mmol), BuLi (1.6M in hexane, 6.9 mL, 10.3 mmol), $ZnCl_2$ (1M in THF, 10.9 mL, 10.9 mmol), compound **C2** (2.50 g, 6.42 mmol), $Pd(PPh_3)_4$ (148 mg, 0.128 mmol) and THF (50 mL). Purification by FC yielded the title compound (1.77 g, 57%).

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (F6)

Prepared as described for compound **F1** but from compound **E2** (1.69 g, 4.4 mmol), 2-chloro-4,5-dimethylphenol (1.05 g, 6.6 mmol), azodicarboxyl dipiperidide (1.67 g, 6.6 mmol), tributylphosphine (2.2 mL, 8.8 mmol) and toluene (45 mL). Purification of the residue by FC yielded the title compound (1.73 g, 76%). LC-MS: R_t = 1.38; ES+: 516.24.

Compounds of type G

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G1)

To a sol. of compound **F1** (742 mg, 1.30 mmol) in EtOH (13 mL) was added aq. 1M NaOH (13 mL). The resulting mixture was stirred for 35 min at 80 °C, then allowed to cool to rt. Aq. 1M HCl (13 mL) was added and the resulting mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:3) led to the title compound (418 mg, 60%). LC-MS: R_t = 1.32 min, ES+ = 534.04.

4-{4-[3-(2-Chlorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G2)

To a sol. of compound **F2** (374 mg, 0.77 mmol) in EtOH (8 mL) was added aq. 1M NaOH (7.7 mL). The resulting mixture was stirred for 35 min at 80 °C, then allowed to cool to rt. Aq. 1M HCl (7.7 mL) was added and the resulting mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:3) led to the title compound (218 mg, 60%). LC-MS: R_t = 1.29 min, ES+ = 472.15.

4-{4-[3-(2,5-Difluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G3)

To a sol. of compound **F3** (378 mg, 0.77 mmol) in EtOH (8 mL) was added aq. 1M NaOH (7.7 mL). The resulting mixture was stirred for 35 min at 80 °C, then allowed to cool to rt. Aq. 1M HCl (7.7 mL) was added and the resulting mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:3) led to the title compound (220 mg, 60%). LC-MS: R_t = 1.25 min, ES+ = 474.17.

4-{4-[3-(2,3,6-Trifluorophenoxy)propyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G4)

As described for compound **G1**, but from compound **F4** (5.23 g, 10.3 mmol), aq. NaOH (1M, 90 mL) and EtOH (90 mL). The title product was used further without chromatographic purification (4.55 g, 89%).

4-{4-[2-(2,3,5-Trimethylphenoxy)ethyl]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G5)

As described for compound **G1**, but from compound **F5** (2.17 g, 4.53 mmol), aq. NaOH (1M, 30 mL) and EtOH (30 mL). The title product was used further without chromatographic purification (1.86 g, 89%).

4-{4-[2-(2-Chloro-4,5-dimethylphenoxy)ethoxy]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (G6)

As described for compound **G1**, but from compound **F6** (1.73 g, 3.3 mmol), aq. NaOH (1M, 33 mL) and EtOH (33 mL). The title product was used further without chromatographic purification. LC-MS: R_t = 1.10; ES+: 502.31.

2-(4-Bromophenyl)eth-1-yl 2,3,5-trimethylphenyl ether (H1)

A mixture of 2-(4-bromophenyl)ethanol (20.0 mL, 143 mmol), 2,3,5-trimethylphenol (31.1 g, 229 mmol), azodicarboxylic dipiperidide (72.1 g, 286 mmol) and tributylphosphine (88 mL; 357 mmol) in toluene (2.00 L) was heated to reflux for 2 h. The mixture was allowed to cool to rt. The mixture was filtered, washed with toluene and the solvents were partially removed under reduced pressure. The residue was diluted with Et_2O and washed with aq. 1M NaOH (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (petroleum ether → Et_2O/petroleum ether 1:3) yielded the title compound (33.1 g, 73%). LC-MS: R_t = 6.95.

1-Bromo-4-[3-(2-methoxybenzyloxy)prop-1-yloxy]benzene (K)

4-Bromophenol (4.32 g, 25.0 mmol) and 1-(3-chloro-propoxymethyl)-2-methoxy-benzene (Vieira E., *et al.*, *Bioorg. Med. Chem. Letters*, **1999**, *9*, 1397) (4.88 g, 22.7 mmoL) were dissolved in DMF (150 mL). NaI (1.50 g, 0.10 mmol) and Cs_2CO_3 (16.3 g, 50.0 mmol) were added. The mixture was heated to 80 °C and stirred for 6 h before it was allowed to cool to rt. After dilution with EtOAc (600 mL) the mixture was washed with water (1x), aq. 1M NaOH (1x), and aq. 1M HCl (1x). The org. extracts were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure. Purification of the residue by FC (Et_2O/petroleum ether 1:9 → 1:4) yielded the title compound (5.66 g, 71%). R_f = 0.60 (Et_2O/heptane 1:1). ^{1}H-NMR ($CDCl_3$): 7.38 - 7.34 (m, 3 H); 7.26 (t, J = 8.7 Hz, 1 H); 6.94 (t, J = 8.7 Hz, 1 H); 6.86 (d, J = 8.2 Hz, 1 H); 6.78 (d, J = 9.0 Hz, 2 H); 4.57 (s, 2 H); 4.07 (t, J = 6.3 Hz, 2 H); 3.81 (s, 3 H); 3.70 (t, J = 6.3 Hz, 2 H); 2.10 (quint., J = 6.3 Hz, 2 H).

1-Benzyl-4-{4-[3-(2-methoxybenzyloxy)propoxy]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid [2-(2-chlorophenyl)ethyl]methylamide (L1)

To a suspension of tetrahydropyridine **D1** (2.25 g, 4.26 mmol) in EtOH (50 mL) NaOH (1M in water, 30 mL) was added. After 4 h the mixture was warmed up to 60 °C and stirred for 5 h. The reaction mixture was allowed to cool to rt, and the pH was adjusted to 7 with aq. 1M HCl. The solvents were removed under reduced pressure and the residue was dried at high vacuum. The dried residue was triturated with EtOH and filtered (3x), the combined filtrates were evaporated under reduced pressure, and the residue was dried at high vacuum. The residue was diluted in $CHCl_3$ (20 mL), and [2-(2-chlorophenyl)ethyl]methylamine (Jaques B.; Wallace R. G., *Tetrahedron*, **1977**, *33*, 581, 1.48 g, 8.72 mmol), DMAP (cat. amount), HOBt (cat. amount) and EDC·HCl (836 mg, 4.36 mmol) were added. After 4 h at rt the mixture was diluted with CH_2Cl_2 and washed with aq. 10% Na_2CO_3 (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 2:3 → 3:2 → EtOAc) gave the title compound (0.48 g, 17%). R_f = 0.13 (EtOAc/heptane 1:1). LC-MS: R_t = 4.24 min, ES+ = 639.33.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5,6-dihydro-2H-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester (R)

A sol. of compound **D3** (17.6 g) in MeOH (400 ml) and 1N NaOH-soln. (250 ml) was heated at 110°c for 1.5 h. The mixture was allowed to cool to rt and aq. 1M HCl was added to reach pH 4, and was extracted with EtOAc (2x150 ml). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. A sol. this crude material (14g), imidazol (9.75g) and TBDMSCl (13.49g) in DMF (80 ml) was stirred at room temperature for 1h. Aq. sat. NH_4Cl (100ml) was added and the mixture was extracted with heptane (3x100ml).).The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. A sol. of this crude product, and K_2CO_3 (2.5 g) in MeOH (50 ml) and water (50 ml) was stirred at room temperature for 1h. Aq. sat. NH_4Cl (100ml) was added and the mixture was extracted with Et_2O

(3x50ml).).The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The crude title product (17.2g, quant. yield) was used in the next step without purification. LC-MS: R_t = 1.12; ES+:478.38.

Compounds of type S

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(2-chloro-3-trifluoromethylbenzyl)cyclopropylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S1)

A sol. of compound **R** (2.62 g, 5.5 mmol), (2-chloro-3-trifluoromethylbenzyl)-cyclopropylamine (2.74 g, 11.0 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL) was stirred overnight. The mixture was washed with aq. 1M HCl (3x) and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:9 → 1:4 → 1:3) yielded the title compound (2.95 g, 75%). R_f = 0.55 (EtOAc/heptane 1:1). LC-MS: R_t = 7.68.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3,5-difluorobenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S2)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(3,5-difluorobenzyl)amine (2.01 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.83 g, 79%). LC-MS: R_t = 1.20; ES+: 643.23.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S3)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(2,3-dichlorobenzyl)amine (2.38 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.02 g, 53%). LC-MS: R_t = 1.20; ES+: 675.15.

5-[(2-Bromobenzyl)cyclopropylcarbamoyl]-4-{4-[2-(*tert*-butyldimethyl-silanyloxy)ethoxy]phenyl}-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S4)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), (2-bromobenzyl)cyclopropylamine (2.49 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.02 g, 53%). LC-MS: R_t = 1.26; ES+: 687.41.

4-{4-[2-(tert-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(2,3-dimethylbenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S5)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(2,3-dimethylbenzyl-amine (1.93 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.25 g, 64%). LC-MS: R_t = 1.26; ES+: 635.53.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3-trifluoromethoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S6)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(3-trifluoromethoxybenzyl)amine (2.54 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.51 g, 66%). LC-MS: R_t = 1.26; ES+: 691.48.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3-methylbenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S7)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), cyclopropyl-(3-methylbenzyl)amine (1.77 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.14 g, 62%). LC-MS: R_t = 1.25; ES+: 621.54.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(3-chlorobenzyl)-cyclopropylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S8)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), (3-chlorobenzyl)cyclopropylamine (1.99 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.44 g, 69%). LC-MS: R_t = 1.26; ES+: 641.44.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(2-chlorobenzyl)-ethylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S9)

As described for compound **S1**, but from compound **R** (2.62 g, 5.5 mmol), (2-chlorobenzyl)ethylamine (1.87 g, 11 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.67 mL, 22.0 mmol), HOBt (817 mg, 6.05 mmol) and EDC·HCl (1.58 g, 8.25 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (2.31 g, 67%). LC-MS: R_t = 1.25; ES+: 629.45.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(2-fluoro-5-methoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S10)

As described for compound **S1**, but from compound **R** (2.59 g, 5.42 mmol), cyclopropyl-(2-fluoro-5-methoxybenzyl)amine (2.12 g, 10.8 mmol), DMAP (132 mg, 1.12 mmol), DIPEA (3.70 mL, 21.7 mmol), HOBt (732 mg, 5.42 mmol) and EDC·HCl (1.56 g, 8.13 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (2.21 g, 62%).

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(6-chlorobenzo[1,3]-dioxol-5-ylmethyl)cyclopropylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S11)

As described for compound **S1**, but from compound **R** (2.41 g, 5.05 mmol), (6-chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylamine (2.28 g, 10.1 mmol), DMAP (123 mg, 1.01 mmol), DIPEA (3.50 mL, 20.2 mmol), HOBt (682 mg, 5.05 mmol) and EDC·HCl (1.45 g, 7.58 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (1.97 g, 57%).

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S12)

As described for compound **S1**, but from compound **R** (2.80 g, 5.86 mmol), cyclopropyl-(3,5-dimethoxybenzyl)amine (2.43 g, 11.7 mmol), DMAP (143 mg, 1.17 mmol), DIPEA (3.00 mL, 17.6 mmol), HOBt (792 mg, 5.86 mmol) and EDC·HCl (1.68 g, 8.79 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (2.97 g, 76%). LC-MS: $R_t = 1.23$; ES+ = 667.1.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3-methoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S13)

As described for compound **S1**, but from compound **R** (2.80 g, 5.86 mmol), cyclopropyl-(3-methoxybenzyl)amine (2.08 g, 11.7 mmol), DMAP (143 mg, 1.17 mmol), DIPEA (3.00 mL, 17.6 mmol), HOBt (792 mg, 5.86 mmol) and EDC·HCl (1.68 g, 8.79 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (2.68 g, 72%). LC-MS: $R_t = 1.23$; ES+ = 637.3.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[cyclopropyl-(3,4-dimethoxybenzyl)carbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S14)

As described for compound **S1**, but from compound **R** (2.48 g, 5.19 mmol), cyclopropyl-(3,4-dimethoxybenzyl)amine (2.15 g, 10.4 mmol), DMAP (127 mg, 1.04 mmol), DIPEA (3.60 mL, 20.8 mmol), HOBt (700 mg, 5.19 mmol) and EDC·HCl (1.49 g, 7.79 mmol) in CH_2Cl_2 (50 mL). Purification by FC yielded the title compound (2.92 g, 84%). LC-MS: $R_t = 1.23$; ES+ = 637.3.

4-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-5-[(2-chlorobenzyl)-cyclopropylcarbamoyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (S15)

As described for compound **S1**, but from compound **R** (3.82 g, 8.00 mmol), (2-chlorobenzyl)cyclopropylamine (4.36 g, 24.0 mmol), DMAP (195 mg, 1.60 mmol), DIPEA (5.50 mL, 32.0 mmol), HOBt (1.08 g, 8.00 mmol) and EDC·HCl (2.30 g, 12.0 mmol) in CH_2Cl_2 (70 mL). Purification by FC yielded the title compound (3.10 g, 60%). LC-MS: R_t = 1.26; ES+ = 641.4.

Compounds of type T

5-[(2-Chloro-3-trifluoromethylbenzyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T1)

A sol. of compound **S1** (2.95 g, 4.16 mmol) and TBAF (1M in THF, 6.24 mL, 6.24 mmol) in THF (15 mL) was stirred at rt for 90 min. The mixture was diluted with EtOAc and washed with brine (1x), water (1x) and brine again (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 2:3 → 3:2 → 4:1) yielded the title compound (1.56 g, 63%). R_f = 0.10 (EtOAc/heptane 1:1) were collected. LC-MS: R_t = 5.63; ES+ = 595.37.

5-[Cyclopropyl-(3,5-difluorobenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T2)

As described for compound **T1**, but from compound **S2** (2.83 g, 4.40 mmol), TBAF (1M in THF, 6.60 mL, 6.60 mmol) and THF (15 mL). Purification by FC yielded the title compound (0.95 g, 41%). LC-MS: R_t = 5.16; ES+ = 529.48.

5-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T3)

As described for compound **T1**, but from compound **S3** (2.47 g, 3.66 mmol), TBAF (1M in THF, 5.48 mL, 5.48 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.43 g, 70%). LC-MS: R_t = 5.52; ES+ = 561.31.

5-[(2-Bromobenzyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T4)

As described for compound **T1**, but from compound **S4** (2.02 g, 2.95 mmol), TBAF (1M in THF, 4.42 mL, 4.42 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.40 g, 83%). LC-MS: R_t = 5.22; ES+ = 571.32.

5-[Cyclopropyl-(2,3-dimethylbenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T5)

As described for compound **T1**, but from compound **S5** (2.25 g, 3.54 mmol), TBAF (1M in THF, 5.32 mL, 5.32 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.74 g, 94%). LC-MS: R_t = 5.32; ES+ = 521.68.

5-[Cyclopropyl-(3-trifluoromethoxybenzyl)carbamoyl]-4-[4-(2-hydroxy-ethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T6)

As described for compound **T1**, but from compound **S6** (2.51 g, 3.63 mmol), TBAF (1M in THF, 5.45 mL, 5.45 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.94 g, 93%). LC-MS: R_t = 1.04; ES+ = 577.32.

5-[Cyclopropyl-(3-methylbenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T7)

As described for compound **T1**, but from compound **S7** (2.14 g, 3.45 mmol), TBAF (1M in THF, 5.20 mL, 5.20 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.66 g, 95%). LC-MS: R_t = 5.19; ES+ = 507.58.

5-[(3-Chlorobenzyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T8)

As described for compound **T1**, but from compound **S8** (2.44 g, 3.80 mmol), TBAF (1M in THF, 5.70 mL, 5.70 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.71 g, 85%). LC-MS: R_t = 5.25; ES+ = 527.37.

5-[(2-Chlorobenzyl)ethylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T9)

As described for compound **T1**, but from compound **S9** (2.31 g, 3.67 mmol), TBAF (1M in THF, 5.50 mL, 5.50 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.40 g, 74%). LC-MS: R_t = 5.19; ES+ = 559.06.

5-[Cyclopropyl-(2-fluoro-5-methoxybenzyl)carbamoyl]-4-[4-(2-hydroxy-ethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T10)

As described for compound **T1**, but from compound **S10** (1.97 g, 2.87 mmol), TBAF (1M in THF, 5.75 mL, 5.75 mmol) and THF (20 mL). Purification by FC yielded the title compound (1.50 g, 97%). LC-MS: R_t = 5.02; ES+ = 541.46.

5-[(6-Chlorobenzo[1,3]dioxol-5-ylmethyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T11)

As described for compound **T1**, but from compound **S11** (2.20 g, 3.37 mmol), TBAF (1M in THF, 6.75 mL, 6.75 mmol) and THF (25 mL). Purification by FC yielded the title compound (1.58 g, 82%). LC-MS: R_t = 5.28; ES+ = 571.34.

5-[Cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T12)

As described for compound **T1**, but from compound **S12** (2.97 g, 4.45 mmol), TBAF (1M in THF, 8.90 mL, 8.90 mmol) and THF (30 mL). Purification by FC yielded the title compound (2.14 g, 87%). LC-MS: R_t = 0.99; ES+ = 553.2.

5-[Cyclopropyl-(3-methoxybenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T13)

As described for compound **T1**, but from compound **S13** (2.68 g, 4.21 mmol), TBAF (1M in THF, 8.40 mL, 8.40 mmol) and THF (30 mL). Purification by FC yielded the title compound (2.03 g, 92%). LC-MS: R_t = 0.97; ES+ = 523.2.

5-[Cyclopropyl-(3,4-dimethoxybenzyl)carbamoyl]-4-[4-(2-hydroxyethoxy)-phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T14)

As described for compound **T1**, but from compound **S14** (2.92 g, 4.38 mmol), TBAF (1M in THF, 8.80 mL, 8.80 mmol) and THF (30 mL). Purification by FC yielded the title compound (2.02 g, 83%). LC-MS: R_t = 0.96; ES+ = 553.21.

5-[(2-Chlorobenzyl)cyclopropylcarbamoyl]-4-[4-(2-hydroxyethoxy)phenyl]-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (T15)

As described for compound **T1**, but from compound **S15** (3.10 g, 4.84 mmol), TBAF (1M in THF, 10.3 mL, 10.3 mmol) and THF (40 mL). Purification by FC yielded the title compound (2.35 g, 92%). LC-MS: R_t = 1.02; ES+ = 527.14.

Preparation of the final compounds

Preparation of Example 8 is given in a detailed description. The other examples depicted in Table 1 can be prepared in analoguous procedures.

Example 8

4-{4-[3-(2-Bromo-5-fluorophenoxy)propyl]phenyl}-1,2,5,6-tetrahydro-pyridine-3-carboxylic acid cyclopropyl-(2-*p*-tolylethyl)amide trifluoroacetate salt

According to the general procedures A and B, starting from compound **G1** and cyclopropyl-(2-*p*-tolylethyl)amine. LC-MS: $R_t = 0.95$ min, ES+ = 591.38.

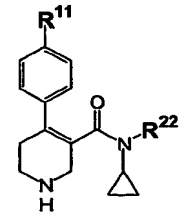
The following examples listed in Table 1 serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Activities are classified as follows:

Activity class A: IC_{50} (Plasmepsin II) < 100 nM

Activity class B: 100 nM < IC_{50} (Plasmepsin II) < 10 μM

Table 1:



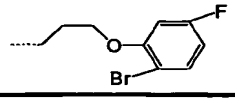
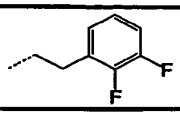
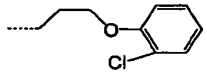
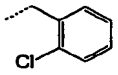
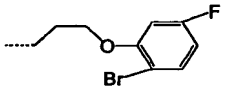
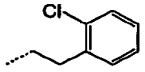
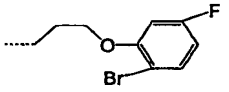
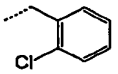
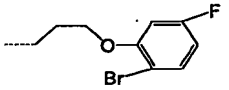
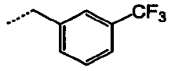
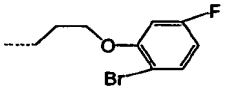
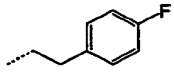
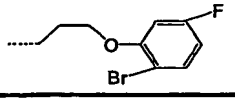
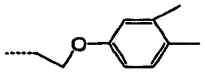
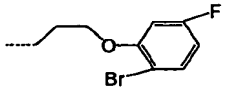
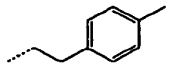
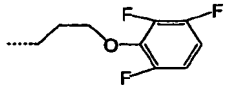
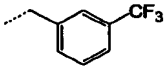
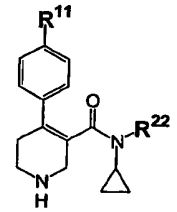
Ex. No.	R^{11}	R^{22}	Activity Class
1			A
2			A
3			A
4			A
5			B
6			B
7			B
8			B
9			B

Table 1 continued:



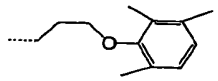
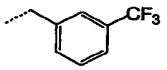
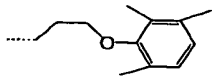
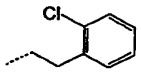
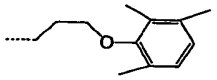
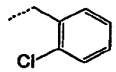
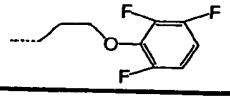
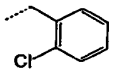
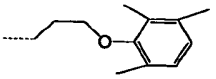
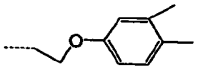
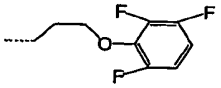
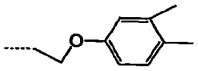
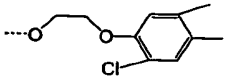
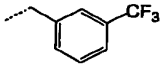
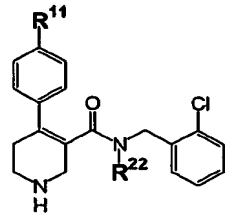
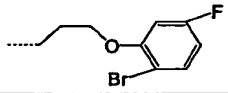
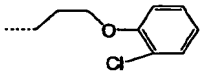
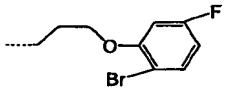
Ex. No.	R^{11}	R^{22}	Activity Class
10			B
11			B
12			B
13			B
14			B
15			B
16			B

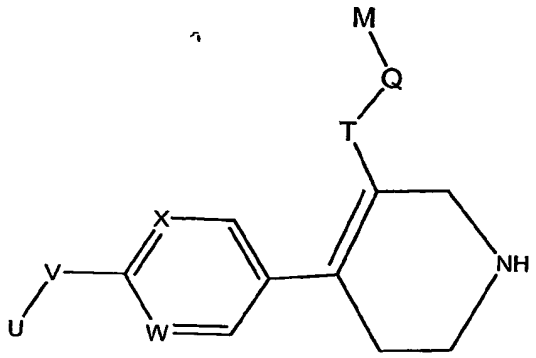
Table 1 continued:



Ex. No.	R^{11}	R^{22}	Activity Class
17			B
18			B
19			A

Claims

1. Pharmaceutical compositions for treating diseases demanding the inhibition of parasite aspartic proteases containing one or more compound(s) of the general formula **I**,



General formula I

wherein

X and W represent independently a nitrogen atom or a CH-group;

V represents $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; $-CH_2-CH_2-A-CH_2-CH_2-B-$;

A and B independently represent -O- ; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; -COO-; $-(CH_2)_pOCONR^1-$; $-(CH_2)_pN(R^{1'})CONR^1-$;

Q represents lower alkylene; lower alkenylene;

M represents hydrogen; cycloalkyl; aryl; heterocyclyl; heteroaryl;

R^1 and $R^{1'}$ independently represent hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

p is the integer 1, 2, 3 or 4;
r is the integer 3, 4, 5, or 6;
s is the integer 2, 3, 4 or 5;
t is the integer 1, 2, 3 or 4;
u is the integer 1, 2 or 3;
v is the integer 2, 3 or 4;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms and suitable carrier materials.

2. Pharmaceutical compositions according to claim 1 for treatment of disorders associated with the role of plasmepsin II and which require inhibition of plasmepsin II for treatment.

3. Pharmaceutical compositions according to claim 1 for treatment or prevention of malaria.

4. Pharmaceutical compositions according to claim 1 for treatment or prevention of diseases caused by protozoal infection.

5. Pharmaceutical compositions according to claim 1 which contain aside of one or more compounds of the general formula I a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor.

6. Use of pharmaceutical compositions according to any one of claims 1 to 5 for treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases

7. Use of pharmaceutical compositions according to any one of claims 1 to 5 for treatment or prevention of malaria.

8. Use of pharmaceutical compositions according to any one of claims 1 to 5 for treatment or prevention of protozoal infections.

9. Use of pharmaceutical compositions according to any one of claims 1 to 5 for treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases in combination with a known plasmepsin II inhibitor, a known antimalarial or a known HIV protease inhibitor or another known anti-HIV treatment.

10. Use of a compound of formula I in claim 1 for the preparation of a medicament for the treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases.

11. Use according to claim 10 wherein said disease is malaria.

12. Use according to claim 10 wherein said disease is protozoal infection.

13. Use of a compound of formula I in claim 1 for the preparation of a medicament for the treatment or prevention of diseases demanding the inhibition of parasitic aspartic proteases in combination with a known plasmepsin II

inhibitor, a known antimalarial or a known HIV protease inhibitor or another known anti-HIV treatment.

14. A method of treating a patient suffering from a disease requiring the inhibition of parasitic aspartic proteases by administering a pharmaceutical composition according to any one of claims 1 to 5.

15. A method according to claim 11 by administering a dose of the parasitic aspartic protease inhibitor of the general formula I between 1 mg and 1000 mg per day.

16. A method according to claim 11 by administering a dose of the parasitic aspartic protease inhibitor of the general formula I between 1 mg and 500 mg per day.

17. A method according to claim 11 by administering a dose of the parasitic aspartic protease inhibitor of the general formula I between 5 mg and 200 mg per day.

18. A process for the preparation of a pharmaceutical composition according to any one of the claims 1 to 5, characterized by mixing one or more active ingredients according to claim 1 with inert excipients in a manner known per se.